IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Maes, et al.

Serial No.: 09/773,351 Group Art Unit: 1617

Filed: January 31, 2001 Examiner: Jiang, Shaojia A.

For: Cholesterol Sulfate and Amino Sugar Compositions for Enhancement of Stratum Corneum Function

REMARKS

The Examiner rejects Claims 1 and 3 to 20 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-21 of copending Application No. 10/424,616. The claims of the copending Application are believed to be still pending. Applicants again acknowledge the provisional double patent rejection made by the Examiner. However, in light of the arguments set forth below, Applicants will make a terminal disclaimer, if necessary, in the event that allowable subject matter is indicated.

A. Claims Are Limited to an Integral Mixture in a Vehicle

In the present office action, the Examiner notes that the present claims are not limited to "the act of mixing produce a mixture" [*sic*] with respect to both the novelty rejection over U.S. Patent No. 5,650,166 ("the '166 Ribier reference") and the obviousness rejection over U.S. Patent Nos. 5,925,364 and 5,411,742 ("the '364 and the '742 references"). Further, the Examiner questions what orderly manner is used to form discrete layers of a vesicle dispersed in the aqueous phase. Thus, the Examiner acknowledges that the cited references teach discrete layers of a vesicle dispersed in the aqueous phase. However, according to the Examiner, the present claims only recite a composition comprising a mixture of effective amounts of cholesterol sulfate or salts, integral with or mixed with an exfoliant in a vehicle. The Examiner again finds that the features that Applicants argue and assert are not in the rejected claims. In response, Applicants assert that the claims previously, and as amended in the present response to further enhance the clarity, are directed to the very claim limitation, an integral mixture in a vehicle, which is missing from the cited references. To advance prosecution, the present claims are amended to precisely state "an integral mixture." Specifically, Claim 1 as amended reads as follows.

1 (currently amended): A composition for topical application to the skin comprising **an integral mixture** of cholesterol sulfate or salts thereof present in an amount between 0.05 to about 5.00 percent,

with an exfoliant present in an amount between 0.1 to about 10.0 percent **in a cosmetically or pharmaceutically acceptable vehicle**.

The Examiner in the present office action acknowledges that the cited references teach discrete layers. Applicants assert that regardless of the method used to achieve their formation, discrete layers are not integral with each other, and therefore, the present claims containing this limitation are not obvious in view of the cited references. It is not necessary to limit the claims to either "the act of mixing to produce a mixture" or to a specific method in specific method steps. Based on the cited references, one of ordinary skill in the art would expect to make vesicles with discrete layers by mixing and not the vehicle containing the mixture of integral components of the present invention. Because the product of the present invention is different than the alleged product taught by the cited references, the present claims as amended are adequately directed to limitations that are not disclosed by the cited references. If an inventor takes steps that the prior art suggests cannot be made, it is probative of non-obviousness. *Yamanouchi Pharm. Co. v. Danbury Pharmacal Inc.*, 21 F. Supp. 2d 366, 374 n. 15, 48 USPQ2d 1741, 1748 n. 15 (S.D. N.Y. 1998), *aff'd*, 231 F.3d 1339, 56 USPQ2d 1641 (Fed. Cir. 2000). It is not permissible to pick and choose only so much of any given reference as will support a given position and ignore the reference in its totality." *Lubrizol Corp. V. Exxon Corp.*, 986 F. supp. 302, 322, 7 USPQ2d 1513, 1527 (N.D. Ohio 1988).

While Applicants refrain from speculating on a specific method for forming separate lipid layers, Applicants note that it is indicated in the '742 reference at column 1, lines 38 to 54, that ionic amphiphilic lipids possess the property of forming mesomorphic phases and are capable of swelling in an aqueous solution to form a lamellar phase. After stirring in the presence of an aqueous solution, '742 amphiphilic lipids form vesicles dispersed in the aqueous solution. Further, in the Summary of the Invention in the '364 reference, the alleged invention is described as being oily globules that are coated and dispersed in an aqueous phase. In other words, the '364 oily globules are encapsulated, and thus, the contents of the ionic lipids in the lamellar phase are not mixed with, but rather are separated from the aqueous phase. Further, the teaching of cholesterol sulphate in the '364 reference is with respect to the coating for the oily globule as taught at column 2, lines 37 to 41, wherein it states that "each oily globule is individually coated with a . . . layer obtained from . . . at least one ionic amphiphilic lipid." Cholesterol sulphate is provided as an exemplary ionic amphiphilic lipid at column 3, lines 43 to 55. As cholesterol sulphate is part of the coating of the oily globule, there is no integral mixture with an exfoliant formed by the teachings of the '364 reference. The potential exfoliants cited by the Examiner include salicylic acid, at column 15, line 6 and keratolytic agents at column 14, line 49. However, in

both of these examples they are lipophilic actives contained inside the '364 oily globule. The '364 lipophilic actives are, therefore, not integrally mixed with the coating on the oily globule.

Similar to the '742 reference, the '364 preparation does not produce a mixture because the ionic lipids swell under the action of mixing to form discrete layers of a lipid vesicle which separates its contents from the other ingredients in the composition, namely the outside media (e.g., the aqueous phase). The Examiner notes that the '364 reference fails to disclose linoleic acid and cholesterol. However, these compounds are not disclosed in the present claims, and it is not clear why this is pointed out. Specifically, one of ordinary skill in the art would not substitute cholesterol with cholesterol sulfate. In support of this assertion, Applicants submit herewith a declaration by Philip Wesley Wertz ("the Wertz Declaration") associated with Application No. 08/865,821 for its pertinence to the distinct nature of cholesterol and cholesterol sulfate. In paragraph 5, of the Wertz Declaration, the declarant makes the following statement.

> One of ordinary skill in the art recognizes that cholesteryl esters, cholesterol, and cholesteryl sulphate and phosphate are distinct compounds and treats each of these compounds as non-equivalent compounds due to their distinct distribution in the stratum corneum as well as their different functions in the stratum corneum.

Therefore, the Examiner's reliance on the teaching of cholesterol in the cited references is misplaced. It would not have been obvious nor does the combination of linoleic acid, cholesterol and exfoliant in the cited references make the present invention. Therefore, there is no teaching or suggestion in the '364 reference or the '742 reference, alone or combined, of an integral mixture like that of the present invention, as amended, and Applicants request that this rejection be withdrawn.

2. An Integral Mixture is Not a Lipid Vesicle

As previously discussed in Applicants' last response, none of the cited references teaches or suggests an integral mixture. There is no need to place emphasis on the methods of making either the lipid vesicles of the cited prior art or the integral mixture of the present invention. The focus should be on the two starkly different end products created in the cases of the cited prior art and of the present invention. Contrary to the present invention, the act of mixing in the cited references causes the ionic lipid to swell and arrange itself in an orderly manner to form separate and discrete layers of a vesicle dispersed in the aqueous phase. Thus, the ionic lipid used with other materials to make the vesicle is not integrally mixed with the content of the aqueous phase; but, rather is used to form separate and discrete entities present in the outside media (i.e., the aqueous phase). They do not form an integral mixture as an end product. The vesicle holds active agents within and keeps the actives separate from media outside of

its walls. Creating a vesicle is akin to encapsulation where the actives inside and the materials used to encapsulate are not integrally mixed with the outside media. Therefore, the combination of the '364 Ribier reference and the '742 reference fails to teach or suggest the present invention, as amended, of the integral mixture in a cosmetic or pharmaceutical vehicle.

The Examiner concludes this rejection by stating that "it is irrelevant whether the [cited] reference includes those features [in the claims] or not, so long as the prior art discloses a composition comprising the same ingredients." In support of this, the Examiner cites *In re Van Geuns*, 26 USPQ2d 1057 (Fed. Cir. 1993) (hereinafter referred to as "*Van Geuns*"). However, Applicants argue first, that the cited prior art does not disclose the present compositions, and second, that this case does not apply to the present situation because the limitation at issue is present in the claims. In *Van Geuns*, the limitation of an NMR or MRI apparatus was not present in the claims. This is unlike the present case where the limitation, of being an integral mixture in the vehicle, has been and still is present in the claims. Therefore, this case does not apply to the present situation because it is not necessary to read the limitation of an integral mixture in a vehicle from the specification into the claims.

C. Present invention is distinct from cited prior art

The Examiner argues that the '166 compositions are a mixture of the ingredients in the present invention. However, this is simply not the case. The '166 compositions are vesicles that would not be recognized by one of ordinary skill in the art as a mixture. In the present invention, as amended, an integral mixture of ingredients is in a cosmetic or pharmaceutical vehicle. Unlike the present invention, the '166 compositions are discrete layers in an aqueous phase. This is taught in the '166 reference at column 1, line 65 to column 2, line 13, and column 1, lines 24 to 30, where it is explained that the '166 compositions are two types of lipid vesicles and that lipid vesicles are understood by one of ordinary skill in the art to be particles formed of a membrane of concentric lamellae where the lamellae contain bimolecular layers of amphiphilic lipids encapsulating an aqueous phase just as described in the '364 reference above. Thus, like the '364 reference, the '166 end product of a vesicle is indeed different than the present invention and the arguments presented above in relation to the '364 reference apply likewise to the '166 reference. Applicants have asserted and assert again herein that the method and/or method steps for achieving the end result is irrelevant as long as the arrangement of the ingredients in the final product are distinct from what is described in the prior art as in the '166 reference. The elements in the '166 Ribier reference are not arranged as they are in claims of the present invention and this has not been addressed. It is not necessary to know how or why the elements in the '166 reference end up being arranged as they are. What is at issue here is that the '166

elements are not arranged as an integral mixture in a cosmetic or pharmaceutical vehicle, and therefore, the '166 reference fails to teach or suggest the present invention.

Contrary to the Examiner's assertion, the arrangement in the '166 Ribier reference is not an "integral mixture" in a vehicle as one of ordinary skill in the art would understand it. Two ingredients that are separated from one another, as they are in the '166 Ribier by virtue of the vesicle formation, are not integral with one another. The Examiner has previously admitted in the office action of September 10, 2004, page 2, that a mixture can be interpreted by one of ordinary skill in the art as being integral with. Therefore, Applicants assert that one of ordinary skill in the art would understand that the present invention as amended is an integral mixture distinct from the separate lipid bilayers of the '166 Ribier reference. There is no integration where there is separation. Although the steps to preparing the '166 lipid bilayers involve a stirring step, there is no disclosure that the ingredients simply stirred are added to a cosmetic or pharmaceutical vehicle at the conclusion of the stirring step. Rather, the '166 reference discloses at column 7, line 43 to column 8, line 14, stirring to form separate lipid bilayers that can then be added to an aqueous phase. The vesicles formed in the '166 reference are defined at column 1, lines 23 to 29 and include bimolecular layers. Additional hydration and/or dialysis treatment steps are also disclosed in the '166 reference. Therefore, the '166 Ribier reference does not anticipate the claims of the present invention because it fails to disclose an integral mixture of cholesterol sulphate and an exfoliant in a vehicle. In deciding the issue of anticipation, two steps must be taken: first, the elements of the claims must be identified to determine their meaning in light of the specification; and second, the corresponding elements disclosed in the allegedly anticipating reference must be identified. *Lindemann Maschinenfabrik GMBG v. Am. Hoist and Derrick Co. et al.*, 221 USPQ 481, 485; *Cf. Slimfold Mfg. Co. v. Kinkead Indus., Inc.*, 810 F.2d 1113, 1116, 1 USPQ2d 1563, 1566 (Fed. Cir. 1987). As the second step has not been taken and cannot be taken because an integral mixture of cholesterol sulfate and an exfoliant in a vehicle is not found in the '166 Ribier reference, Applicants request that the rejection of the claims based on anticipation be withdrawn.

The limitations of the present claims sufficiently describe an integral mixture of components in a vehicle which one of ordinary skill in the art would recognize as being distinct and separate from the same components physically located in separate bilayers of a liposome (or vesicle) as they are in the '166 Ribier reference. Applicants have not found that this point has been addressed. "A proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out [the claimed process], those of ordinary skill would have a reasonable expectation of success." *In re*

Vaeck, 20 USPQ2d 1438, 1442 (CAFC 1991); see *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). These two factors have not been met in the present case.

First, there is no teaching or suggestion in the prior art to make a mixture of the pertinent components in the '166 Ribier reference. The teaching in the '166 Ribier reference of the components physically separated by bilayers of a vesicle is contrary and opposite to the integral mixture of the same components of the present invention. In a mixture, the components are not separated; but rather, are integrated. Since the '166 Ribier reference only teaches the components in a state of separation, the mixture of the present invention is not taught or suggested by the '166 Ribier reference.

The second factor of the obviousness analysis is likewise not met because the '166 Ribier reference fails to reveal that making the composition of the present invention, namely the integral mixture of the components in a vehicle, would be expected by one of ordinary skill in the art to have reasonable success. This factor is linked to the first factor because as long as there is no teaching or suggestion in the '166 Ribier reference to make the integral mixture in a vehicle of the present invention, there likewise, cannot be a reasonable expectation of success to do what is not taught or suggested. But beyond this, the teachings of the '166 Ribier reference are aimed at treating two different layers of the skin at the same time. Thus, the components of the '166 Ribier compositions start out separated in the composition and the components remain separated as they are directed to two different areas of the skin. There is never an integral mixing of the components in a cosmetic or pharmaceutical vehicle in the '166 Ribier reference. This is illustrated by the teaching at column 1, lines 11 to 14, where the '166 Ribier compositions are described as comprising at least one active agent conveyed via at least two distinct types of lipid vesicles. Additional support is found at column 2, lines 19 to 21, of the '166 Ribier reference wherein it is taught that the alleged invention involves two different agents to act in different areas of the skin. The different agents act in different areas due to the different lipid vesicles containing them. The different vesicles are classified based on the different types of action (see column 2, lines 34 to 41.) Every aspect of the '166 Ribier compositions relates to being separate and distinct. Thus, the '166 Ribier reference does not teach, suggest, nor motivate one of ordinary skill in the art to make the compositions of the present invention having integrally mixed components in a cosmetic or pharmaceutical vehicle.

Establishment of a *prima facie* case of obviousness requires, *inter alia*, that prior art references teach or suggest ***all claim limitations***. *CFMT Inc. v. Yieldup International Corp.*, 68 USPQ2d 1940 (CAFC 2003) citing *In re Royka*, 490 F.2d 981, 985, 180 USPQ 580 (CCPA 1974) (obviousness requires a suggestion of all limitations in a claim); *see also In re Gulack*, 703 F.2d 1381, 1385 n.9, 217 USPQ 401 (Fed. Cir. 1983). As the limitation of an integral mixture in a cosmetic or

pharmaceutical vehicle is recited in the present claims and yet is not taught or suggested by any of the cited references, Applicants assert that a *prima facie* case of obviousness has not been made and request that the rejection under 35 U.S.C. §103(a) be withdrawn.

According to the Examiner, the '166 Ribier reference in combination with U.S. Patent No. 6,150,381 issued to Subbiah ("the '381 reference") and in further view of U.S. Patent No. 5,702,691 issued to Ichinose et al. ("the '691 reference") renders Claims 10 to 12 and 20 obvious. As noted above, the present claims as amended are directed to an integral mixture of cholesterol sulfate in certain amounts with an exfoliant in certain amounts in a cosmetic or pharmaceutical vehicle. The '381 reference teaches sclareolide-like compounds for treating disorders caused by microbials such as, for example, bacteria, and one specific disorder is acne. As disclosed in the '381 reference, topical formulations containing sclareolide are generally prepared by admixing sclareolide in water and at least one organic solvent. However, this does not remedy the defect of the '166 reference discussed above. Since the '166 reference teaches lipid vesicles encapsulating water soluble actives, the combination of these references at most suggests that sclareolide could be incorporated within the aqueous phase of the '166 lipid vesicles (i.e., sclareolide could be encapsulated). Because lipid vesicles are not simple admixtures, the combination of the '166 reference and the '381 reference fails to teach or suggest the present invention. Finally, the '691 reference teaches flavanonol derivatives in hair nourishing and hair growth products and is cited by the Examiner for its teaching of the anti-inflammatory properties of white birch extract. However, like that of the '381 reference, the teachings of the '691 reference do nothing to remedy the defect of the '166 reference. In order to make out a *prima facie* case of obviousness, it must be shown that there is a suggestion or a teaching to one of ordinary skill in the art to make the combination of cited references or a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Essentially, none of the cited references alone or in combination teach or suggest an integral mixture of cholesterol sulfate and an exfoliant in a cosmetic or pharmaceutical vehicle as an end product. Applicants, therefore, request that the rejections for obviousness be withdrawn.

Finally, Applicants point out that the burden to provide evidence of unexpected results does not pass from the Examiner to Applicants until a *prima facie* case of obviousness has been made. In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Rijckaert*, 28 USPQ2d 1955, 1956 (CAFC 1993) (citing *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)). Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant. *Id.* "A *prima facie* case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art." *Id.,* (citing *In re Bell* , 991 F.2d 781, 782, 26

USPQ2d 1529, 1531 (Fed. Cir. 1993) (quoting *In re Rinehart*, 531 F.2d 1048, 1051, 189 USPQ 143, 147 (CCPA 1976)). Since a *prima facie* case of obviousness has not been made, for reasons which are discussed above, the burden of coming forward with evidence or data regarding inherent properties has not shifted to Applicants.

Even if the interpretation of one of ordinary skill in the art were that a lipid vesicle containing cholesterol sulfate in the membrane layer and NADG encapsulated therein was equivalent to the integral mixture of the present invention, Applicants assert that it would be rebutted by the surprising results of the present invention. The Examiner asserts in the final office action that the Example in the present specification provides no clear and convincing evidence of nonobviousness or unexpected results since it is not a direct comparison between the present invention and the cited prior art references. However, Applicants previously note that all evidence of nonobviousness must be considered. *In re Soni*, 44 USPQ2d 1684, 1687 (Fed. Cir. 1995). Unexpected results must be sufficient to overcome a clear and convincing showing of obviousness. *Richardson-Vicks Inc. v. The Upjohn Co.*, 44 USPQ2d 1181, 1188 (CAFC 1997). As previously noted, a clear and convincing showing of obviousness has not been made. However, even if such a showing were made, comparative test results are not the only evidence that can be presented to overcome a clear and convincing showing of obviousness. The unexpected result in the present invention lies in the fact that two opposite acting agents are combined and do not cancel out their activity.

As Applicants have pointed out above and in previous responses, the systems in the cited prior art and that of the present invention are not the same, and there is no reason to believe that the integral mixture of the ingredients directly in a vehicle would necessitate a comparison with a lipid vesicle as these are two completely different systems and different arrangements of the components. To support this fact, Applicants previously submitted a copy of an article, Bouwstra et al., "Cholesterol sulfate and calcium affect stratum corneum lipid organization over a wide temperature range" Journal of Lipid Research, vol. 40, 2303-3212 (Dec. 1999). In the article, the authors note that reduced levels of cholesterol sulfate contribute to desquamation, thus indicating that the presence of cholesterol sulfate would maintain the integrity of the stratum corneum and prevent desquamation. Therefore, Applicants maintain that one of ordinary skill in the art would expect a combination of cholesterol sulfate and an exfoliant to have no effect on the surface on the skin because while the exfoliant would contribute to desquamation, the cholesterol sulfate would act to prevent desquamation.

To recapitulate, the present invention is based on the finding that two ingredients, the cholesterol sulfate and the exfoliant, although they have opposing activities, when added as a mixture to a pharmaceutical or cosmetic vehicle, do not neutralize one another's activities, but rather their activity

occurs in tandem, and can improve or maintain a healthy skin barrier. As previously mentioned, this benefit cannot even be addressed with the cited references because these two materials form lipid vesicles, and therefore, are not in fact mixed. Rather, they are separated such that one, the cholesterol sulfate, is part of a protective membrane that encases the other, the NADG. The whole point of the lipid vesicles/lamellar systems of the cited references is to protect and prevent the active inside from being exposed to anything else. Thus, a comparison of this kind would be futile.

Applicants submit herewith an Information Disclosure Statement. An Information Disclosure Statement ("IDS") dated January 31, 2001 and a Supplemental IDS dated January 5, 2004 were previously filed. Enclosed herewith is a Second Supplemental IDS for six references each of which are being submitted before the mailing date of a final action pursuant to 37 C.F.R. 1.97(c). Applicants believe that none of the references submitted in the Supplemental IDS anticipate or render obvious the present invention.

CONCLUSION

The present invention, as amended, is an integral mixture of an exfoliant and a cholesterol sulfate in a cosmetic or pharmaceutical vehicle that is not taught or suggested by the cited references describing lipid vesicles having one bilayer containing N-acetyl D-glucosamine, and another bilayer containing cholesterol sulfate as the components are arranged differently. Because none of the cited references alone nor in combination would lead one of ordinary skill in the art to the compositions and methods of the present invention, a *prima facie* case of obviousness has not been established. Applicants request therefore, that the Examiner's rejections under 35 U.S.C. §§102 and 103 be withdrawn. In view of the arguments presented above in the present submission, the claims are believed to be in condition for allowance, and issuance of a Notice of Allowance is respectfully solicited.

Respectfully submitted,

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